IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. A-60179-2/DJB/TAL

Anticipated Classification of this Application:

Class: Subclass:

Prior Application: 08/459,134

Examiner: E. Webman

Art Unit: 1615

"EXPRESS MAIL" MAILING LABEL NUMBER TB156452604 US
DATE OF DEPOSIT 24 Sept. 1998
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: BOX PATENT APPLICATION FEE, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

TYPED NAME Geody Domingo

SIGNED

Box PATENT APPLICATION FEE
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This is a request for filing an

___ Original
_X_ Continuation
___ Divisional
___ Continuation-in-part

application under 37 C.F.R. 1.53(b), in the name of Vernon G. Wong and Frank Kochinke (Names of ALL Applicants), for IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS (Title of Invention). This _X_ continuation ___ divisional ___ continuation-in-part claims priority to pending application Serial No. 08/459,134, filed on June 2, 1995.

1. (a) ___ Enclosed is a new application.
   (b) ___ Enclosed is a continuation-in-part application.
   (c) _X_ Enclosed is a copy of the prior application.

2. (a) ___ Enclosed is a new Declaration.

(b) X Enclosed is a copy of the prior executed Declaration as originally filed.

(c) ___ Enclosed is a Combined Declaration/Power of Attorney.

3. (a) ___ Enclosed is a Small Entity Affidavit.

(b) X A Small Entity Affidavit is of record in the prior application.

4. X The filing fee is calculated below:

Claims as filed in the prior application, less any claims canceled by amendment below:

FOR:	(Col. 1) NO. FILED	(Col. 2) NO. EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY FEE
BASIC FEE				$395	OR		$790
TOTAL CLAIMS	20 -20 =	* 0	x11 =	$ 0	OR	x22 =	$ 0
INDEP CLAIMS	4 -3 =	* 1	x41 =	$ 41	OR	x82 =	$ 0
[ ] MULTIPLE DEPENDENT CLAIM PRESENTED			+135 =	$ 0	OR	+270 =	$ 0
			TOTAL	$436	OR	TOTAL	$ 0

*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

5. X The Commissioner is hereby authorized to charge any additional fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. 06-1300 (Order No. A-60179-1/DJB/TAL).

6. X Our check in the amount of $436.00 is enclosed.

7. _____ Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one independent claim must be retained for filing purposes.)

8. X Amend the specification by inserting before the first line the sentence:

--This is a X continuation ___ division ___ continuation-in-part of application Serial No. 08/459,134 filed June 2, 1995--

9. (a) X Informal drawings are enclosed, 4 sheets.

(b) _____ Formal drawings are enclosed, ___ sheets.

10. (a) _____ Priority of application Serial No. _____ filed on _____ in _____ is claimed under 35 U.S.C. 119.

(b) _____ The certified copy has been filed in prior application Serial No. _____ filed on _____.

11. _____ An Assignment is enclosed.

12. __X__ The prior application is assigned of record to _____ Oculex Pharmaceuticals, Inc. _____.

13. _____ A Power of Attorney by Assignee is enclosed.

14. _____ The power of attorney in the prior application is to:

_____
(name)

_____
(address)

_____

(a) __X__ The power appears in the original papers in the prior application.

(b) ___ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

(c) ___ Address all future communications to:

Todd A. Lorenz, Esq.
FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP
Suite 3400, Four Embarcadero Center
San Francisco, California 94111-4187
Telephone: (415) 781-1989

15. __X__ A preliminary amendment is enclosed. (Claims added by this amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.)

16. _____ A Prior Art Statement is enclosed.

17. __X__ I hereby verify that the attached papers are a true duplicate of prior application Serial No. 08/459,134 originally filed on June 2, 1995 .

Date: 9/23/98

Todd A. Lorenz
Registration No. 39,754

Address of Signer:

__X__ Attorney or agent of record

_____ Filed under Section 1.34(a)

FLEHR HOHBACH TEST
ALRBITTON & HERBERT, LLP
4 Embarcadero Center, Suite 3400
San Francisco, CA 94111

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A-60179-2/DJB/TAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Wong and Kochinke
Serial No.: Group No.: 1615
Filed: Examiner: E. Webman
Entitled: **IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to an examination on the merits, please amend the accompanying continuing application under 37 C.F.R. § 1.53(b) as follows:

The Commissioner is hereby authorized to charge any additional fees, including extension fees, to Deposit Account No. 06-1300 (Order No. A-60179-1/DJB/TAL).

IN THE CLAIMS:

Please cancel Claims 1-9.

Please add the following new claims:

10. An implant for controlled, sustained drug release comprising:

a pharmacologically acceptable biodegradable polymer which is degraded at the site of implantation, wherein said biodegradable polymer comprises at least about 20 weight percent of the implant;

a therapeutically active agent at a concentration from 10 to 50 weight percent of the implant;

a release modulator at a concentration from 10 to 50 weight percent of the implant;

wherein said implant is an anhydrous solid structure which releases said therapeutically active agent at the site of implantation within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days after implantation.

11. An implant according to Claim 10, wherein said release modulator is a hydrophilic entity and said therapeutically active agent is a hydrophobic entity.

12. An implant according to Claim 11, wherein said release modulator is hydroxypropylmethylcellulose.

13. An implant according to Claim 10, wherein said anhydrous solid structure is a particle, sheet, patch, plaque, fiber, microcapsule, microsphere or disc.

14. An implant according to Claim 10, wherein said release modulator is a hydrophobic entity and said therapeutically active agent is a hydrophilic entity.

15. An implant according to Claim 10, wherein said release modulator is a therapeutically active agent.

16. An implant according to Claim 15, wherein said active agent is a steroid and said release modulator is a water soluble antibiotic.

17. An implant according to Claim 15, wherein said active agent is a non-steroidal antiinflammatory drug and said release modulator is a water soluble antibiotic.

18. An implant according to Claim 10, wherein said biodegradable polymer is poly-lactate glycolate acid copolymer.

19. An implant for controlled, sustained drug release comprising:

poly-lactate glycolic acid copolymer at a concentration of at least about 20 weight percent of the implant;

a therapeutically active antiinflammatory drug at a concentration from 10 to 50 weight percent of the implant;

a release modulator at a concentration from 10 to 50 weight percent of the implant;

wherein said implant is an anhydrous solid structure which releases said therapeutically active antiinflammatory within a therapeutic dosage that does not vary by more than about 100% for a period of at least about 3 days.

20. An implant for controlled, sustained drug release comprising:

poly-lactate glycolic acid copolymer at a concentration of at least about 20 weight percent of the implant;

a therapeutically active steroid at a concentration from 10 to 50 weight percent of the implant;

a release modulator at a concentration from 10 to 50 weight percent of the implant;

wherein said implant is an anhydrous solid structure which is degraded at the site of implantation and releases said therapeutically active steroid within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days after implantation.

21. An implant according to Claim 20, wherein said release modulator is hydroxypropylmethylcellulose.

22. An implant according to Claim 20, wherein said anhydrous solid structure is a particle, sheet, patch, plaque, fiber, microcapsule, microsphere or disc.

23. An implant according to Claim 20, where said release modulator is a therapeutically active agent.

24. An implant according to Claim 23, wherein said release modulator is a water soluble antibiotic.

25. An implant for controlled, sustained drug release comprising:

poly-lactate glycolic acid copolymer at a concentration of at least about 20 weight percent of the implant;

a therapeutically active non-steroidal antiinflammatory drug at a concentration from 10 to 50 weight percent of the implant;

a release modulator at a concentration from 10 to 50 weight percent of the implant;

wherein said therapeutically active non-steroidal antiinflammatory drug is released within a therapeutic dosage that does not vary by more than about 100% for a period of at least about 3 days.

26. An implant according to Claim 25, wherein said release modulator is hydroxypropylmethylcellulose.

27. An implant according to Claim 25, wherein said anhydrous solid structure is a particle, sheet, patch, plaque, fiber, microcapsule, microsphere or disc.

28. An implant according to Claim 25, wherein said release modulator is a therapeutically active agent.

29. An implant according to Claim 28, wherein said release modulator is a water soluble antibiotic.

IN THE SPECIFICATION

At page 7, line 26, after "months", please insert the following sentence:

--The therapeutically active agent is released within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days.--

At page 19, "Abstract of the Invention," on lines 11-12, change "substantially constant rate of release" to --controlled, sustained release--.

REMARKS

The above amendments to the specification and claims are consistent with amendments made and/or proposed in the parent application, U.S. Ser. No. 08/459,134. No new matter is added. In the claim amendments, support for the term 'anhydrous" may be found in the teachings of Example 1 on pages 13-15 of the specification. Support for the term "solid structure" may be found on page 8, lines 7-13 and further at page 12, lines 13-28. In the amendments to the specification, the term "therapeutically active agent is released within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days" is found in originally-filed claims 1 and 9. Support for the language "controlled, sustained drug release" may be found on page 2, line 27.

If, in the opinion of the Examiner, a telephone call would help expedite the prosecution of the instant application, the Examiner is invited to contact the undersigned at (45) 781-1989.

Dated: September 24, 1998

Todd A. Lorenz
Registration No. 39,754
FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP
4 Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone (415) 781-1989

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IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS

INTRODUCTION

Technical Field

Biodegradable implants formulated for controlled, sustained drug release.

Background of the Invention

Solid pharmaceutically active implants that provide sustained release of an active ingredient are able to provide a relatively uniform concentration of active ingredients in the body. Implants are particularly useful for providing a high local concentration at a particular target site for extended periods of time. These sustained release forms reduce the number of doses of the drug to be administered, and avoid the peaks and troughs of drug concentration found with traditional drug therapies. Use of a biodegradable drug delivery system has the further benefit that the spent implant need not be removed from the target site.

Many of the anticipated benefits of delayed release implants are dependent upon sustained release at a relatively constant level. However, formulations of hydrophobic drugs with biodegradable matrices may have a release profile which shows little or no release until erosion of the matrix occurs, at which point there is a dumping of drug.

The eye is of particular interest when formulating implantable drugs, because one can reduce the amount of surgical manipulation required, and provide effective

levels of the drug specifically to the eye. When a solution is injected directly into the eye, the drug quickly washes out or is depleted from within the eye into the general circulation. From the therapeutic standpoint, this may be as useless as giving no drug at all. Because of this inherent difficulty of delivering drugs into the eye, successful medical treatment of ocular diseases is inadequate.

Improved sustained release formulations which allow for a constant drug release rate are of considerable interest for medical and veterinary uses.

Relevant Literature

U.S. Patents 4,997,652 and 5,164,188 disclose biocompatible implants for introducing into an anterior chamber or posterior segment of an eye for the treatment of an ocular condition.

Heller, Biodegradable Polymers in Controlled Drug Delivery, in: CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 1, CRC Press, Boca Raton, FL, 1987, pp 39-90, describes encapsulation for controlled drug delivery. Heller in: Hydrogels in Medicine and Pharmacy, N.A. Peppes ed., Vol. III, CRC Press, Boca Raton, FL, 1987, pp 137-149, further describes bioerodible polymers.

Anderson et al., Contraception (1976) **13**:375 and Miller et al., J. Biomed. Materials Res. (1977) **11**:711, describe various properties of poly(dL-lactic acid). U.S. Patent 5,075,115 discloses sustained release formulations with lactic acid polymers and co-polymers.

Di Colo (1992) Biomaterials **13**:850-856 describes controlled drug release from hydrophobic polymers.

SUMMARY OF THE INVENTION

Compositions and methods are provided for biodegradable implants formulated to provide a controlled, sustained drug release. The release rate is modulated by combining in the implant hydrophobic and hydrophilic agents. The release modulator

may act to accelerate or retard the rate of release. Optionally, the modulator will be a therapeutically active agent. The invention provides a sustained release implant having a combination of active agents with a defined release profile.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows the release profile of a hydrophobic drug from an extended release drug delivery system. Figure 1B shows the release profile of the same drug when formulated in a drug delivery system with a release modulator.

Figure 2A shows the release profile of dexamethasone in the absence or presence of the release modifier, ciproflaxacin HCl. Figure 2B shows the release of ciprofloxacin in the presence of dexamethasone. Figure 2C shows the release of ciprofloxacin in the absence of a release modifier. Figure 2D shows the releae profile from a drug delivery system having combined hydrophilic and hydrophobic drugs, and further having a pharmaceutically inactive release modifier.

Figure 3 shows a cross-sectional view of an eye.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

A controlled drug release is achieved by an improved formulation of slow release biodegradable implants. The release rate of a drug from an implant is modulated by addition of a release modulator to the implant. Release of a hydrophobic agent is increased by inclusion of an accelerator in the implant, while retardants are included to decrease the release rate of hydrophilic agents. The release modulator may be physiologically inert, or a therapeutically active agent.

The rate of release of the therapeutically active agent will be controlled by the rate of transport through the polymeric matrix of the implant, and the action of the modulator. By modulating the release rate, the agent is released at a substantially constant rate, or within a therapeutic dosage range, over the desired period of time.

The rate of release will usually not vary by more than about 100% over the desired period of time, more usually by not more than about 50%. The agent is made available to the specific site(s) where the agent is needed, and it is maintained at an effective dosage. The transport of drug through the polymer barrier will also be affected by drug solubility, polymer hydrophilicity, extent of polymer cross-linking, expansion of the polymer upon water absorption so as to make the polymer barrier more permeable to the drug, geometry of the implant, and the like.

The release modulator is an agent that alters the release of a drug from a biodegradable implant in a defined manner. It may be an accelerator or a retardant. Accelerators will be hydrophilic compounds, which are used in combination with hydrophobic agents to increase the rate of release. Hydrophilic agents are those compounds which have at least about 100 μg/ml solubility in water at ambient temperature. Hydrophobic agents are those compounds which have less than about 100 μg/ml solubility in water at ambient temperature.

Therapeutically active hydrophobic agents which benefit from release modulation include cyclosporines, *e.g.* cyclosporin A, cyclosporin G, *etc.*; vinca alkaloids, *e.g.* vincristine and vinblastine; methotrexate; retinoic acid; certain antibiotics, *e.g.* ansamycins such as rifampin; nitrofurans such as nifuroxazide; non-steroidal antiinflammatory drugs, *e.g.* diclofenac, keterolac, flurbiprofen, naproxen, suprofen, ibuprofen, aspirin, *etc.* Steroids are of particular interest, including hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, medrysone, fluorometholone, estrogens, progesterones, *etc.*

Accelerators may be physiologically inert, water soluble polymers, *e.g.* low molecular weight methyl cellulose or hydroxypropyl methyl cellulose (HPMC); sugars, *e.g.* monosaccharides such as fructose and glucose, disaccharides such as lactose, sucrose, or polysaccharides such as cellulose, amylose, dextran, *etc.* Alternatively, the accelerator may be a physiologically active agent, allowing for a combined therapeutic

formulation. The choice of accelerator in such a case will be determined by the desired combination of therapeutic activities.

Formulations of particular interest will have a therapeutic combination of two or more active agents, which provides for a sustained release of the agents. Combinations may include steroids, as indicated above, as the hydrophobic agent and water soluble antibiotics, *e.g.* aminoglycosides such as gentamycin, kanamycin, neomycin, and vancomycin; amphenicols such as chloramphenicol; cephalosporins, such as cefazolin HCl; penicillins such as ampicillin, penicillin, carbenicillin, oxycillin, methicillin; lincosamides such as lincomycin; polypeptide antibiotics such as polymixin and bacitracin; tetracyclines such as tetracycline; quinolones such as ciproflaxin, *etc.*; sulfonamides such as chloramine T; and sulfones such as sulfanilic acid as the hydrophilic entity. A combination of non-steroidal anti-inflammatory drugs, as indicated above, with water soluble antibiotics is also of interest. Combinations of anti-viral drugs, e.g. acyclovir, gancyclovir, vidarabine, azidothymidine, dideoxyinosine, dideoxycytosine with steroidal or non-steroidal anti-inflammatory drugs, as indicated above, are of interest. A particular combination of interest is dexamethasone and ciproflaxin.

Release retardants are hydrophobic compounds which slow the rate of release of hydrophilic drugs, allowing for a more extended release profile. Hydrophilic drugs of interest which may benefit from release modulation include water soluble antibiotics, as described above, nucleotide analogs, *e.g.* acyclovir, gancyclovir, vidarabine, azidothymidine, dideoxyinosine, dideoxycytosine; epinephrine; isoflurphate; adriamycin; bleomycin; mitomycin; ara-C; actinomycin D; scopolamine; and the like.

Agents of interest as release retardants include non-water soluble polymers, e.g. high molecular weight methylcellulose and ethylcellulose, *etc.*, low water soluble organic compounds, and pharmaceutically active hydrophobic agents, as previously described.

A combined anti-inflammatory drug, and antibiotic or antiviral, may be further combined with an additional therapeutic agent. The additional agent may be an analgesic, *e.g.* codeine, morphine, keterolac, naproxen, *etc.*, an anesthetic, *e.g.* lidocaine; β-adrenergic blocker or β-adrenergic agonist, *e.g.* ephidrine, epinephrine, etc.; aldose reductase inhibitor, *e.g.* epalrestat, ponalrestat, sorbinil, tolrestat; antiallergic, *e.g.* cromolyn, beclomethasone, dexamethasone, and flunisolide; colchicine. Anihelminthic agents, *e.g.* ivermectin and suramin sodium; antiamebic agents, *e.g.* chloroquine and chlortetracycline; and antifungal agents, *e.g.* amphotericin, *etc.* may be co-formulated with an antibiotic and an anti-inflammatory drug. For intra-ocular use, anti-glaucomas agents, *e.g.* acetozolamide, befunolol, *etc.* in combinations with anti-inflammatory and antimicrobial agents are of interest. For the treatment of neoplasia, combinations with anti-neoplastics, particularly vinblastine, vincristine, interferons α, β and γ, antimetabolites, *e.g.* folic acid analogs, purine analogs, pyrimidine analogs may be used. Immunosuppressants such as azathiprine, cyclosporine and mizoribine are of interest in combinations. Also useful combinations include miotic agents, *e.g.* carbachol, mydriatic agents such as atropine, *etc.*, protease inhibitors such as aprotinin, camostat, gabexate, vasodilators such as bradykinin, etc., and various growth factors, such epidermal growth factor, basic fibroblast growth factor, nerve growth factors, and the like.

The amount of active agent employed in the implant, individually or in combination, will vary widely depending on the effective dosage required and rate of release from the implant. Usually the agent will be at least about 1, more usually at least about 10 weight percent of the implant, and usually not more than about 80, more usually not more than about 40 weight percent of the implant. The amount of release modulator employed will be dependent on the desired release profile, the activity of the modulator, and on the release profile of the active agent in the absence of modulator. An agent that is released very slowly or very quickly will require relatively high amounts of modulator. Generally the modulator will be at least 10, more usually at

least about 20 weight percent of the implant, and usually not more than about 50, more usually not more than about 40 weight percent of the implant.

Where a combination of active agents is to be employed, the desired release profile of each active agent is determined. If necessary, a physiologically inert modulator is added to precisely control the release profile. The drug release will provide a therapeutic level of each active agent.

The exact proportion of modulator and active agent will be empirically determined by formulating several implants having varying amounts of modulator. A USP approved method for dissolution or release test will be used to measure the rate of release (USP 23; NF 18 (1995) pp. 1790-1798). For example, using the infinite sink method, a weighed sample of the drug delivery device is added to a measured volume of a solution containing four parts by weight of ethanol and six parts by weight of deionized water, where the solution volume will be such that the drug concentration is after release is less than 5% of saturation. The mixture is maintained at 37°C and stirred slowly to maintain the implants in suspension. The appearance of the dissolved drug as a function of time may be followed by various methods known in the art, such as spectrophotometrically, HPLC, mass spectroscopy, *etc.* until the absorbance becomes constant or until greater than 90% of the drug has been released. The drug concentration after 1 h in the medium is indicative of the amount of free unencapsulated drug in the dose, while the time required for 90% drug to be released is related to the expected duration of action of the dose *in vivo*. Normally the release will be free of larger fluctuations from some average value which allows for a relatively uniform release, usually following a brief initial phase of rapid release of the drug.

Normally the implant will be formulated to release the active agent(s) over a period of at least about 3 days, more usually at least about one week, and usually not more than about one year, more usually not more than about three months. For the most part, the matrix of the implant will have a physiological lifetime at the site of implantation at least equal to the desired period of administration, preferably at least

twice the desired period of administration, and may have lifetimes of 5 to 10 times the desired period of administration. The desired period of release will vary with the condition that is being treated. For example, implants designed for post-cataract surgery will have a release period of from about 3 days to 1 week; treatment of uveitis may require release over a period of about 4 to 6 weeks; while treatment for cytomegalovirus infection may require release over 3 to 6 months, or longer.

The implants are of dimensions commensurate with the size and shape of the region selected as the site of implantation and will not migrate from the insertion site following implantation. The implants will also preferably be at least somewhat flexible so as to facilitate both insertion of the implant at the target site and accommodation of the implant. The implants may be particles, sheets, patches, plaques, fibers, microcapsules and the like and may be of any size or shape compatible with the selected site of insertion.

The implants may be monolithic, *i.e.* having the active agent homogenously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. Due to ease of manufacture, monolithic implants are usually preferred over encapsulated forms. However, the greater control afforded by the encapsulated, reservoir-type may be of benefit in some circumstances, where the therapeutic level of the drug falls within a narrow window. The selection of the polymeric composition to be employed will vary with the site of administration, the desired period of treatment, patient tolerance, the nature of the disease to be treated and the like. Characteristics of the polymers will include biodegradability at the site of implantation, compatibility with the agent of interest, ease of encapsulation, a half-life in the physiological environment of at least 7 days, preferably greater than two weeks, water insoluble, and the like. The polymer will usually comprise at least about 10, more usually at least about 20 weight percent of the implant.

Biodegradable polymeric compositions which may be employed may be organic esters or ethers, which when degraded result in physiologically acceptable degradation

products, including the monomers. Anhydrides, amides, orthoesters or the like, by themselves or in combination with other monomers, may find use. The polymers will be condensation polymers. The polymers may be cross-linked or non-cross-linked, usually not more than lightly cross-linked, generally less than 5%, usually less than 1%. For the most part, besides carbon and hydrogen, the polymers will include oxygen and nitrogen, particularly oxygen. The oxygen may be present as oxy, *e.g.*, hydroxy or ether, carbonyl, *e.g.*, non-oxo-carbonyl, such as carboxylic acid ester, and the like. The nitrogen may be present as amide, cyano and amino. The polymers set forth in Heller, *supra*, may find use, and that disclosure is specifically incorporated herein by reference.

Of particular interest are polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, and polysaccharides. Included among the polyesters of interest are polymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, polycaprolactone, and combinations thereof. By employing the L-lactate or D-lactate, a slowly biodegrading polymer is achieved, while degradation is substantially enhanced with the racemate. Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic and lactic acid, where either homopolymer is more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of in the implant, where a more flexible implant is desirable for larger geometries.

Among the polysaccharides will be calcium alginate, and functionalized celluloses, particularly carboxymethylcellulose esters characterized by being water insoluble, a molecular weight of about 5 kD to 500 kD, *etc.* Biodegradable hydrogels may also be employed in the implants of the subject invention. Hydrogels are typically a copolymer material, characterized by the ability to imbibe a liquid. Exemplary biodegradable hydrogels which may be employed are described in Heller in: Hydrogels

in Medicine and Pharmacy, N.A. Peppes ed., Vol. III, CRC Press, Boca Raton, FL, 1987, pp 137-149.

Particles can be prepared where the center may be of one material and the surface have one or more layers of the same or different composition, where the layers may be cross-linked, of different molecular weight, different density or porosity, or the like. For example, the center would comprise a polylactate coated with a polylactate-polyglycolate copolymer, so as to enhance the rate of initial degradation. Most ratios of lactate to glycolate employed will be in the range of about 1:0.1 to 1:1. Alternatively, the center could be polyvinyl alcohol coated with polylactate, so that on degradation of the polylactate the center would dissolve and be rapidly washed out of the implantation site.

The formulation of implants for use in the treatment of ocular conditions, diseases, tumors and disorders are of particular interest. The biodegradable implants may be implanted at various sites, depending on the shape and formulation of the implant, the condition being treated, etc. Suitable sites include the anterior chamber, posterior chamber, vitreous cavity, suprachoroidal space, subconjunctiva, episcleral, intracorneal, epicorneal and sclera. Suitable sites extrinsic to the vitreous comprise the suprachoroidal space, the pars plana and the like. The suprachoroid is a potential space lying between the inner scleral wall and the apposing choroid. Implants that are introduced into the suprachoroid may deliver drugs to the choroid and to the anatomically apposed retina, depending upon the diffusion of the drug from the implant, the concentration of drug comprised in the implant and the like. Implants may be introduced over or into an avascular region. The avascular region may be naturally occurring, such as the pars plana, or a region made to be avascular by surgical methods. Surgically-induced avascular regions may be produced in an eye by methods known in the art such as laser ablation, photocoagulation, cryotherapy, heat coagulation, cauterization and the like. It may be particularly desirable to produce such an avascular region over or near the desired site of treatment, particularly where the

desired site of treatment is distant from the pars plana or placement of the implant at the pars plana is not possible. Introduction of implants over an avascular region will allow for diffusion of the drug from the implant and into the inner eye and avoids diffusion of the drug into the bloodstream.

Turning now to Figure 3, a cross-sectional view of the eye is shown, illustrating the sites for implantation in accordance with the subject invention. The eye comprises a lens 16 and encompasses the vitreous chamber 3. Adjacent to the vitreous chamber 3 is the optic part of the retina 11. Implantation may be intraretinal 11 or subretinal 12. The retina is surrounded by the choroid 18. Implantation may be intrachoroidal or suprachoroidal 4. Between the optic part of the retina and the lens, adjacent to the vitreous, is the pars plana 19. Surrounding the choroid 18 is the sclera 8. Implantation may be intrascleral 8 or episcleral 7. The external surface of the eye is the cornea 9. Implantation may be epicorneal 9 or intra-corneal 10. The internal surface of the eye is the conjunctiva 6. Behind the cornea is the anterior chamber 1, behind which is the lens 16. The posterior chamber 2 surrounds the lens, as shown in the figure. Opposite from the external surface is the optic nerves, and the arteries and vein of the retina. Implants into the meningeal spaces 13, the optic nerve 15 and the intraoptic nerve 14 allows for drug delivery into the central nervous system, and provide a mechanism whereby the blood-brain barrier may be crossed.

Other sites of implantation include the delivery of anti-tumor drugs to neoplastic lesions, *e.g.* tumor, or lesion area, *e.g.* surrounding tissues, or in those situations where the tumor mass has been removed, tissue adjacent to the previously removed tumor and/or into the cavity remaining after removal of the tumor. The implants may be administered in a variety of ways, including surgical means, injection, trocar, etc.

Other agents may be employed in the formulation for a variety of purposes. For example, buffering agents and preservatives may be employed. Water soluble preservatives which may be employed include sodium bisulfite, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric

acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol. These agents may be present in individual amounts of from about 0.001 to about 5% by weight and preferably about 0.01 to about 2%. Suitable water soluble buffering agents that may be employed are sodium carbonate, sodium borate, sodium phosphate, sodium acetate, sodium bicarbonate, *etc.*, as approved by the FDA for the desired route of administration. These agents may be present in amounts sufficient to maintain a pH of the system of between 2 to 9 and preferably 4 to 8. As such the buffering agent may be as much as 5% on a weight to weight basis of the total composition. Where the buffering agent or enhancer is hydrophilic, it may also act as a release accelerator, and may replace all or part of the hydrophilic agent. Similarly, a hydrophilic buffering agent or enhance may replace all or part of the hydrophobic agent.

The implants may be of any geometry including fibers, sheets, films, microspheres, circular discs, plaques and the like. The upper limit for the implant size will be determined by factors such as toleration for the implant, size limitations on insertion, ease of handling, etc. Where sheets or films are employed, the sheets or films will be in the range of at least about 0.5 mm x 0.5 mm, usually about 3-10 mm x 5-10 mm with a thickness of about 0.25-1.0 mm for ease of handling. Where fibers are employed, the diameter of the fiber will generally be in the range of 0.05 to 3 mm. The length of the fiber will generally be in the range of 0.5-10 mm. Spheres will be in the range of 2 μm to 3 mm in diameter.

The size and form of the implant can be used to control the rate of release, period of treatment, and drug concentration at the site of implantation. Larger implants will deliver a proportionately larger dose, but depending on the surface to mass ratio, may have a slower release rate. The particular size and geometry of an implant will be chosen to best suit the site of implantation. The chambers, *e.g.* anterior chamber, posterior chamber and vitreous chamber, are able to accomodate relatively large implants of varying geometries, having diameters of 1 to 3 mm. A sheet, or circular

disk is preferable for implantation in the suprachoroidal space. The restricted space for intraretinal implantation requires relatively small implants, having diameters from 0.5 to 1 mm.

In some situations mixtures of implants may be utilized employing the same or different pharmacological agents. In this way, a cocktail of release profiles, giving a biphasic or triphasic release with a single administration is achieved, where the pattern of release may be greatly varied.

Various techniques may be employed to produce the implants. Useful techniques include solvent evaporation methods, phase separation methods, interfacial methods, extrusion methods, molding methods, injection molding methods, heat press methods and the like. Specific methods are discussed in U.S. Patent 4,997,652, herein incorporated by reference. In a preferred embodiment, extrusion methods are used to avoid the need for solvents in manufacturing. When using extrusion methods, the polymer and drug are chosen so as to be stable at the temperatures required for manufacturing, usually at least about 85°C.

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

Example 1

Manufacture and Testing of a Drug Delivery System (DDS) without a Release Modulator

Release of the hydrophobic drug dexamethasone from an extended release drug delivery system was measured. The drug delivery system was made with dexamethasone and polylactic acid/polyglycolic acid copolymer. Dexamethasone powder and a powder of polylactic acid polyglycolic acid (PLGA) copolymer were mixed throughly at a ratio of 50/50. The well mixed powder was filled into an extruder, and heated for 1 hour at 95°C, then extruded through a 20 gauge orifice. Six

DDS of approximately 100-120 μg were cut from the extruded filaments for drug release assessment.

Each individual DDS was placed in a glass vial filled with receptor medium (9% NaCl in water). To allow for "infinite sink" conditions, the receptor medium volume was chosen so that the concentration would never exceed 5% of saturation. To minimize secondary transport phenomena, *e.g.* concentration polarization in the stagnant boundary layer, each of the glass vials was placed into a shaking water bath at 37°C. Samples were taken for HPLC analysis from each vial at defined time points. The HPLC method was as described in USP 23 (1995) pp. 1791-1798. The concentration values were used to calculate the cumulative relase profiles. The release profile is shown in Figure 1A. It is seen that drug release is very slow with this DDS. Appreciable drug release begins in the fourth week after initiation, at approximately the time of polymer disintegration.

Manufacture and Testing of a DDS with HPMC Release Modifier

A drug delivery system was manufactured as described above, except that various concentrations of hydrophilic hydroxypropylmethylcellulose (HPMC) were included as a release modifier. The combinations of drug, polymer and HPMC shown in Table 1 were used.

Table 1

Lot #	PLGA	HPMC	Dexamethasone	Total
XT014	3.5	1.5	5	10
XT015	2	2	5	9
XT013	1.5	1.5	5	8

The release of drug was tested as described above. The data is shown in Figure 1B. It is seen that with the addition of HPMC, there is a pronounced increase in the rate of release. Close to zero order release is observed for XT014 and XT015,

where the ratio of release modulator to drug is 0.3 to 0.4. By selection of the appropriate polymer and release modifier, drug release and delivery interval can be custom-tailored to provide a release profile that is accelerated or retarded.

Example 2

Manufacture and Testing of A DDS with a Pharmaceutically Active Release Modifier

A drug delivery system was manufactured as described in Example 1, except that ciprofloxacin HCl, a pharmaceutically active, hydrophilic compound, was included as a release modifier. The combinations of drug, polymer and HPMC shown in Table 2 were used.

Table 2

Lot #	PLGA	Release Modifier	Drug
XT029	5	-	5 dexamethasone
XT032	4	2 ciprofloxacin	4 dexamethasone
XT030	5	-	5 ciprofloxacin

The release of dexamethasone is increased with the addition of ciprofloxacin HCl, as shown by the data in Figure 2A. The actual drug release is almost doubled when compared to the DDS without a modifier. In addition to the benefits of increased drug delivery, there are therapeutic benefits introduced with the antibiotic activity of ciprofloxacin. The release of ciprofloxacin from from the same DDS is shown in Figure 2B. The release rate is higher than that of dexamethasone. However, the overall release of ciprofloxacin is slower when co-formulated with dexamethasone than it is without dexamethasone, as shown in Figure 2C.

Example 3

Manufacture and Testing of A DDS with Multiple Release Modifiers

A drug delivery system was formulated with hydroxymethylcellulose, cirpofloxacin HCl and dexamethasone, according to the Table 3.

Table 3

Lot #	PLGA	HPMC	Ciprofloxacin	Dexamethasone
XT035	3.4	0.4	2.4	3.8

The data show that after an initial higher release in the first day, an almost zero-order release there after can be observed. The overall release characteristic would be therapeutically acceptable from a therapeutic efficiency aspect.

It is evident from the above results that biodegradable implants formulated with an active agent and release modulator provide for release kinetics where the drug is released at a constant rate over long periods of time, avoiding the need of a patient to administer drugs in much less effective ways, such as topically. The implants provide an improved method of treating ocular and other conditions, by avoiding peaks and troughs of drug release.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An implant for sustained drug release comprising:

a pharmacologically acceptable biodegradable polymer which is degraded at the site of implantation, wherein said biodegradable polymer comprises at least about 20 weight percent of the implant;

a therapeutically active agent at a concentration from 10 to 50 weight percent of the implant;

a release modulator at a concentration from 10 to 50 weight percent of the implant;

wherein said therapeutically active agent is released within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days.

2. An implant according to Claim 1, wherein said release modulator is a hydrophilic entity and said therapeutically active agent is a hydrophobic entity.

3. An implant according to Claim 2, wherein said release modulator is hydroxypropylmethylcellulose.

4. An implant according to Claim 1, wherein said release modulator is a hydrophobic entity and said therapeutically active agent is a hydrophilic entity.

5. An implant according to Claim 1, wherein said release modulator is a therapeutically active agent.

6. An implant according to Claim 5, wherein said active agent is a steroid and said release modulator is a water soluble antibiotic.

7. An implant according to Claim 5, wherein said active agent is a non-steroidal antiinflammatory drug and said release modulator is a water soluble antibiotic.

8. An amplant according to Claim 1, wherein said biodegradable polymer is poly-lactate glycolic acid copolymer.

9. An implant for sustained drug release comprising:

poly-lactate glycolic acid copolymer at a concentration of at least about 20 weight percent of the implant;

methotrexate at a concentration from 10 to 50 weight percent of the implant;

ciprofloxin at a concentration from 10 to 50 weight percent of the implant;

wherein said methotrexate is released within a therapeutic dosage which does not vary by more than about 100% for a period of at least about 3 days.

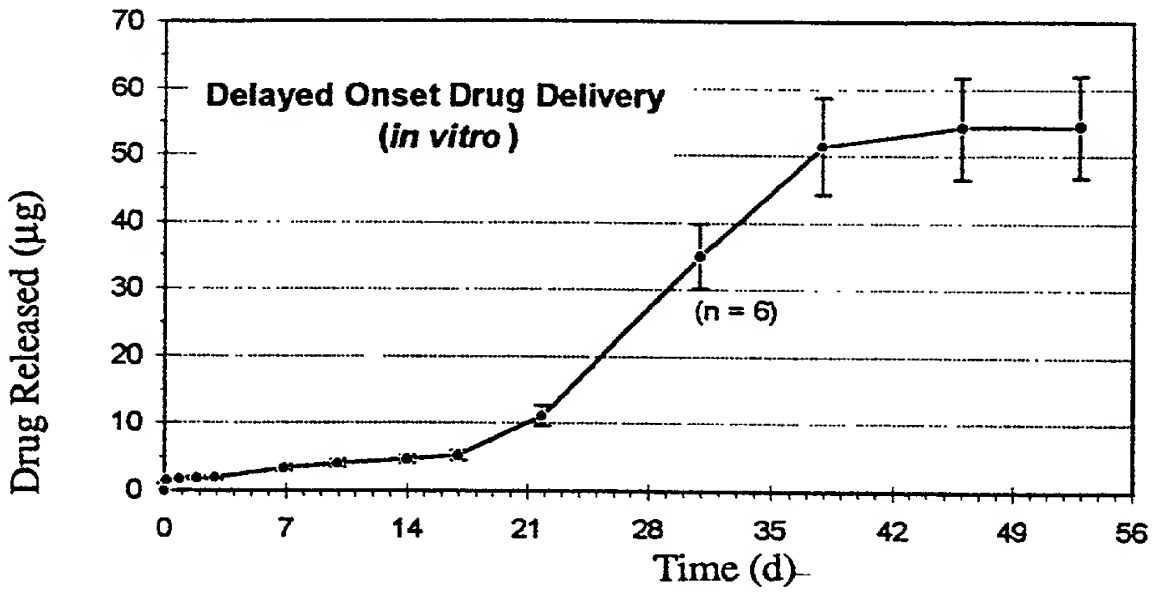
IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS

ABSTRACT OF THE DISCLOSURE

Combinations of hydrophilic and hydrophobic entities in a biodegradable sustained release implant are shown to modulate each other's rate of release. Formulations of a therapeutically active agent and modulator provide substantially constant rate of release for an extended period of time.

Figure 1

A


Delayed Onset Drug Delivery
(in vitro)
Drug Released (µg)
Time (d)
(n = 6)
0
10
20
30
40
50
60
70
0
7
14
21
28
35
42
49
56

B

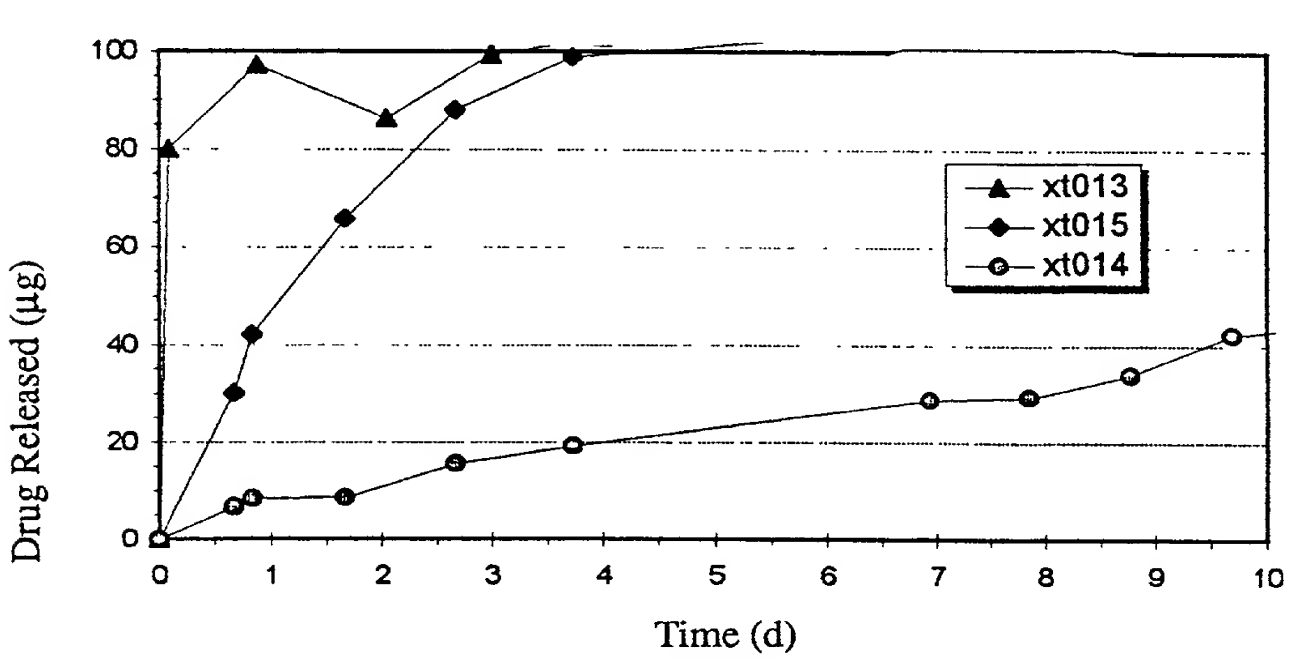
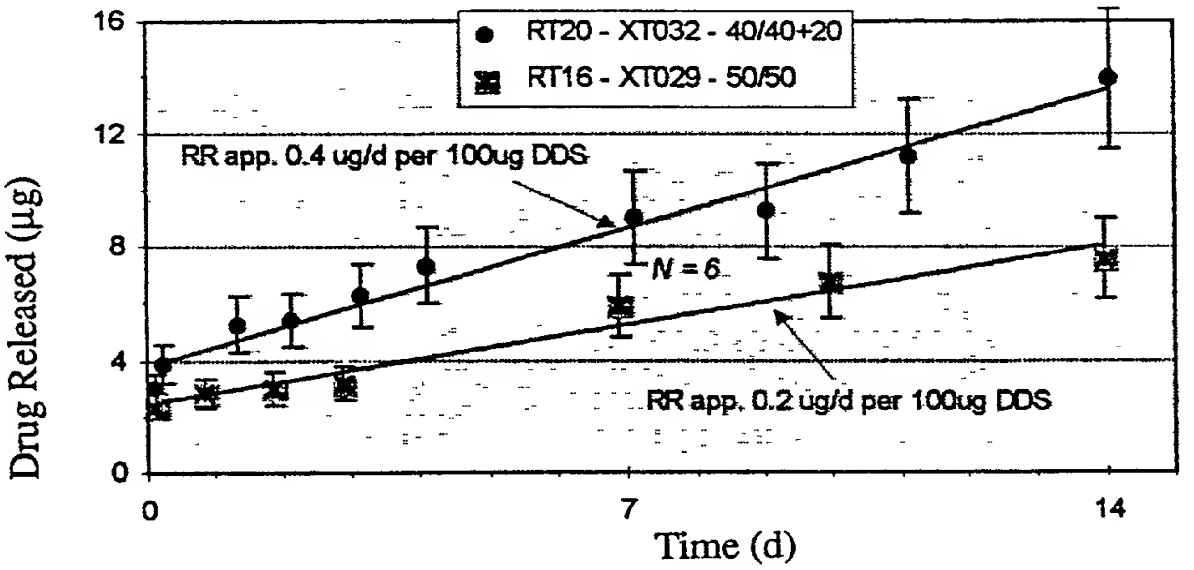

Drug Released (µg)
Time (d)
xt013
xt015
xt014
0
20
40
60
80
100
0
1
2
3
4
5
6
7
8
9
10

Figure 2

A


RT20 - XT032 - 40/40+20
RT16 - XT029 - 50/50
RR app. 0.4 ug/d per 100ug DDS
N = 6
RR app. 0.2 ug/d per 100ug DDS
Drug Released (µg)
Time (d)
0
4
8
12
16
0
7
14

B

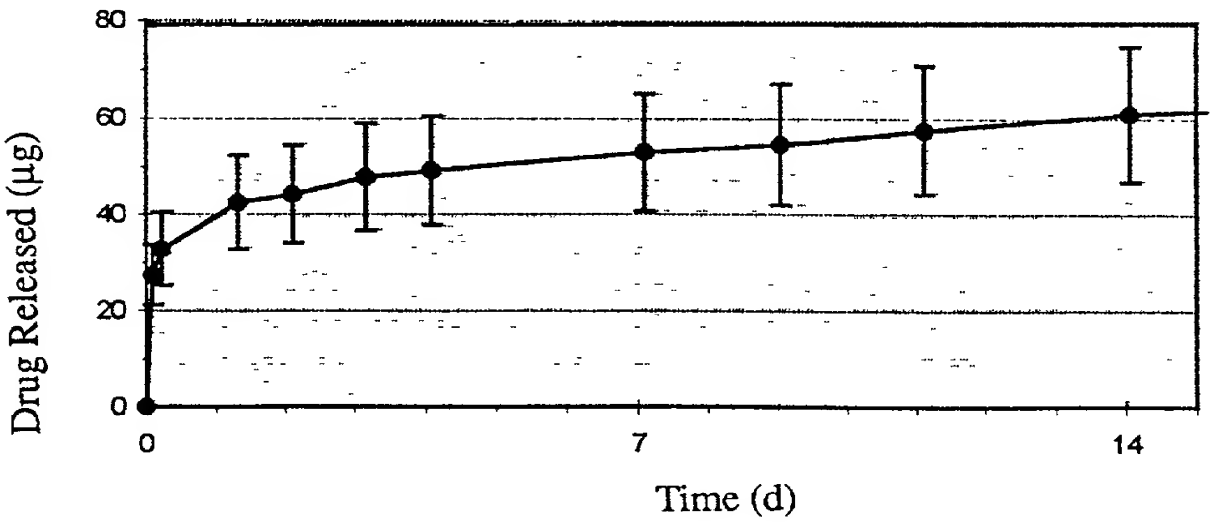
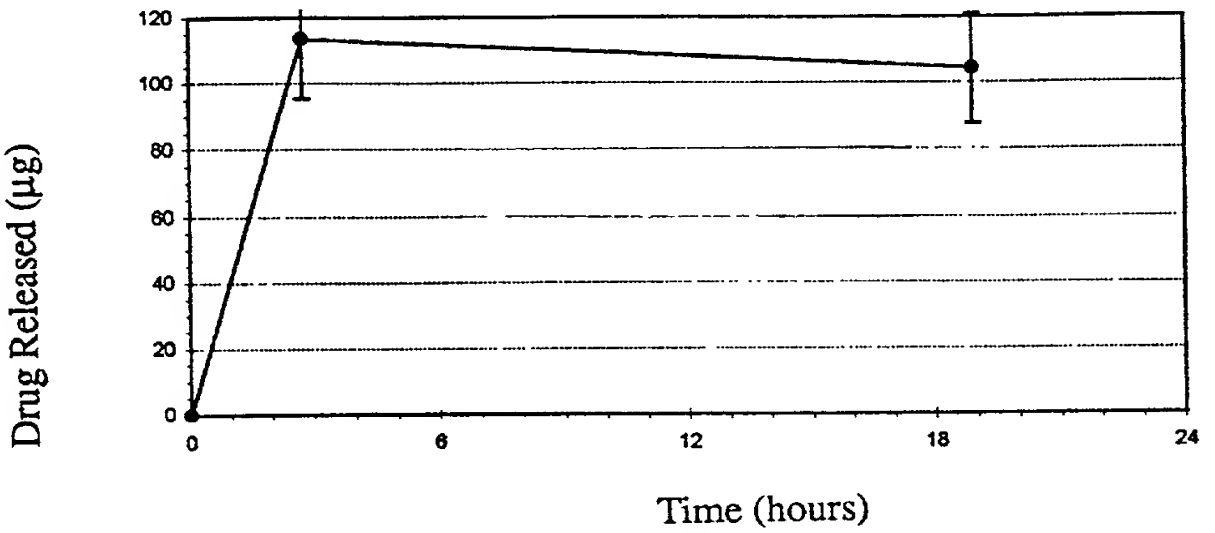
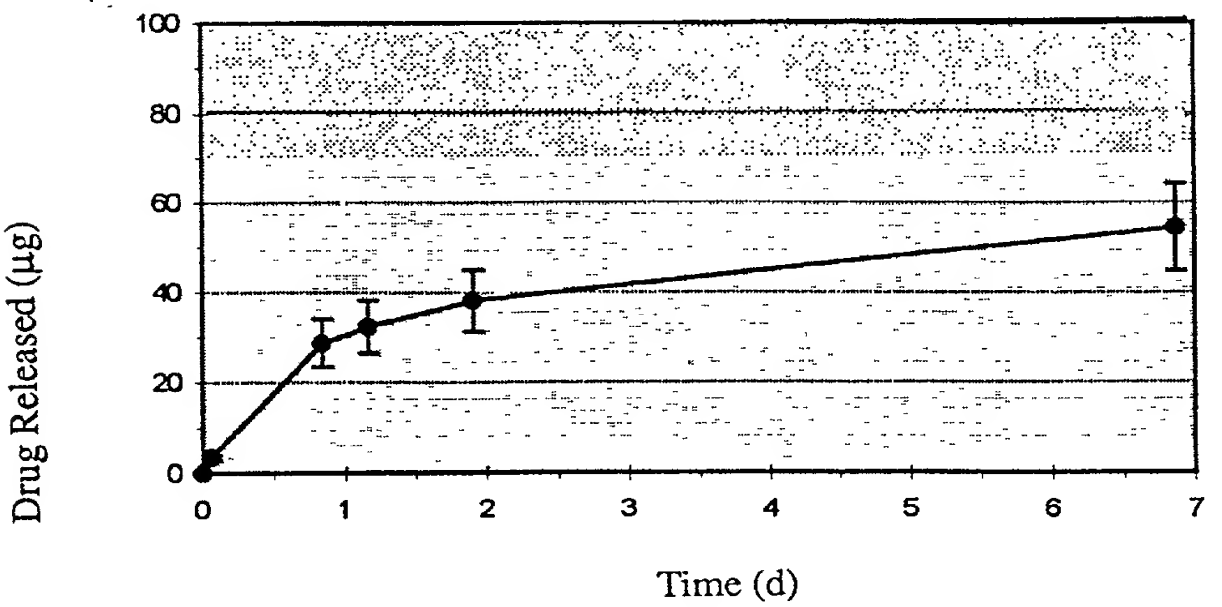

Drug Released (µg)
Time (d)
0
20
40
60
80
0
7
14

Figure 2

C


Drug Released (µg)
120
100
80
60
40
20
0
0
6
12
18
24
Time (hours)

D


Drug Released (µg)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (d)

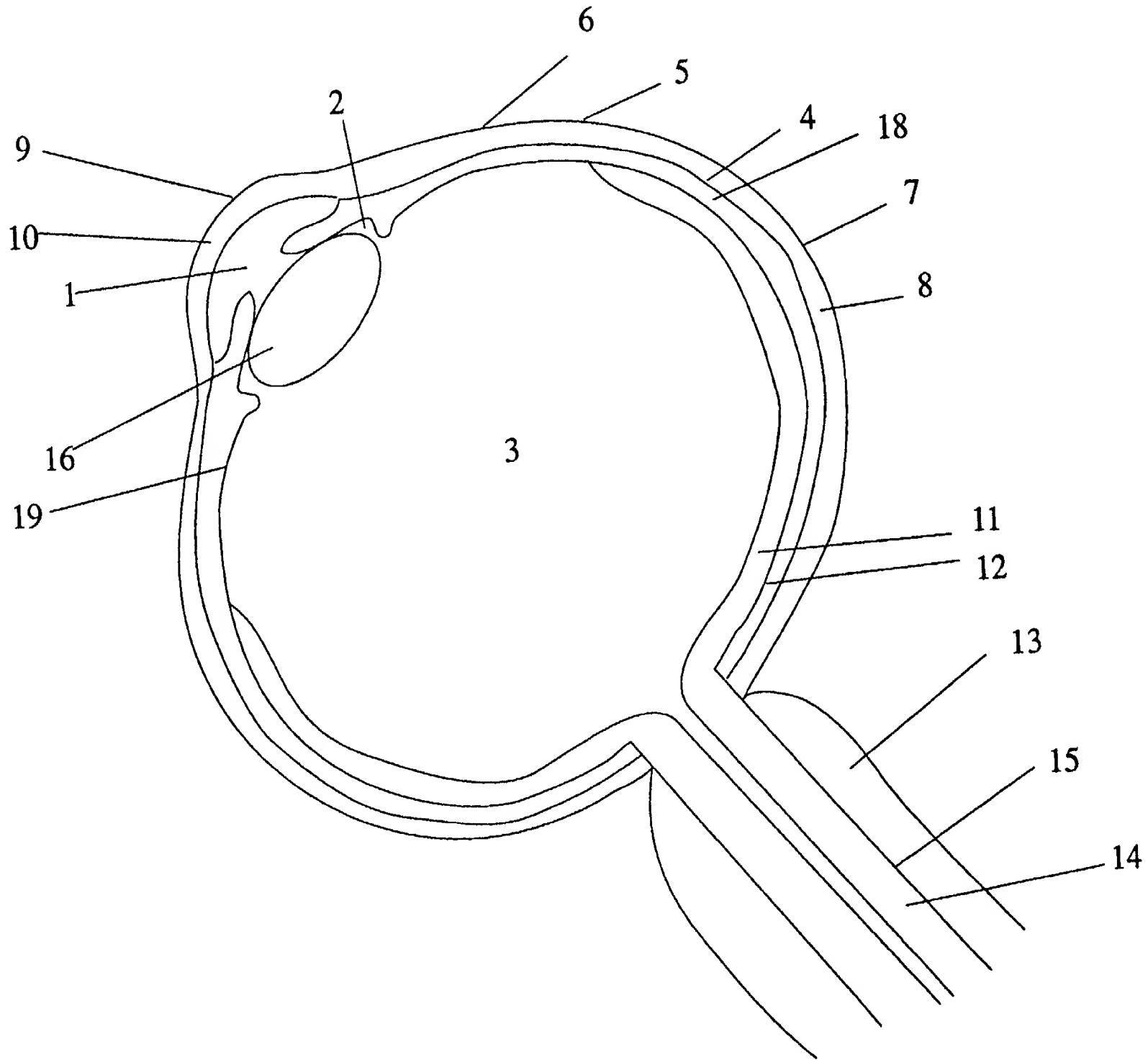


FIGURE 3

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on June 02, 1995 as Application Serial No. 08/459,134 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			☐	☐
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			☐	☐
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			☐	☐
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Harold C. Hohbach, Reg. No. 17,757; Aldo J. Test, Reg. No. 18,048; Thomas O. Herbert, Reg. No. 18,612; Donald N. MacIntosh, Reg. No. 20,316; Jerry G. Wright, Reg. No. 20,165; Edward S. Wright, Reg. No. 24,903; David J. Brezner, Reg. No. 24,774; Richard E. Backus, Reg. No. 22,701; James A. Sheridan, Reg. No. 25,435; Robert B. Chickering, Reg. No. 24,286; Gary S. Williams, Reg. No. 31,066; Richard F. Trecartin, Reg. No. 31,801; C. Michael Zimmerman, Reg. No. 20,451; Walter H. Dreger, Reg. No. 24,190; Steven F. Caserza, Reg. No. 29,780; Bertram I. Rowland, Reg. No. 20,015; Pamela J. Sherwood, Reg. No. 36,677; and Bret E. Field, Reg. No. 37,620; provided that if any one of said attorneys ceases being affiliated with the law firm of Flehr, Hohbach, Test, Albritton & Herbert as partner, employee or of counsel, such attorney's appointment as attorney and all powers derived therefrom shall terminate on the date such attorney ceases being so affiliated.

Direct all telephone calls to PAMELA J. SHERWOOD at (415) 494-8700.

Address all correspondence to:

FLEHR, HOHBACH, TEST,
ALBRITTON & HERBERT
Suite 3400, Four Embarcadero Center
San Francisco, California 94111

File No. A-60179/BIR OCUL-006

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: VERNON WONG

Inventor's signature: [signature]

Date: 6/23/95

Residence: 10908 Rosemont Drive, Rockville, MD 20852

Citizenship: US

Post Office Address: 10908 Rosemont Drive, Rockville, MD 20852

Full name of second joint inventor, if any: FRANK KOCHINKE

Inventor's signature: [signature]

Date: 6/9/95

Residence: 3413 Antonacci Court, San Jose, CA 95148

Citizenship: Germany

Post Office Address: 3413 Antonacci Court, San Jose, CA 95148

Applicant or Patentee: VERNON WONG; FRANK KOCHINKE
Serial or Patent No.: 08/459,134
Filed or Issued: June 02, 1995
Attorney's Docket No.: A-60179/BIR OCUL-006
For: IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

[ ] the owner of the small business concern identified below:
[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN: OCULEX PHARMACEUTICALS, INC.
ADDRESS OF SMALL BUSINESS CONCERN: 3180 Porter Drive, Bldg. 1
Palo Alto, CA 94304-1212

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled, IMPROVED FORMULATION FOR CONTROLLED RELEASE OF DRUGS BY COMBINING HYDROPHILIC AND HYDROPHOBIC AGENTS by inventor(s) VERNON WONG; FRANK KOCHINKE, described in

[ ] the specification filed herewith
[X] application serial no. 08/459,134, filed June 02, 1995
[ ] patent no. _____, issued _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME: _____
ADDRESS: _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME: _____
ADDRESS: _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING JERRY GIN
TITLE IN ORGANIZATION President
ADDRESS OF PERSON SIGNING 3180 Porter Drive, Bldg. 1
Palo Alto, CA 94304-1212

SIGNATURE Jerry Gin DATE 6/9/95

Form 1.27
Rev. 6/92 (PTO Rev. 7/89)